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REPORT FROM

Nordic Lung Congress 2022

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Exercise adaptations and prescription in Asthma

PRESENTED BY MORTEN HOSTRUP, DENMARK

Treatment guidelines for people living with type 2 diabetes, cardiovascular diseases, and obesity, to mention a few, have in decades clearly stated the importance of physical activity as one of the corner stones in the treatment of these patients. This has previously not been the case for treatment guidelines in asthma. There has been a fear that physical activity would lead to acute asthma attacks and, hence it has not been part of treatment guidelines in asthma, it has even been suggested that physical exercise should be avoided by asthmatic patients.

However, research performed during later years has shown that asthmatic patients do have a beneficial effect from physical activity. Furthermore, the presenter stated during the symposia *"-the fact that almost 90% of the Norwegian top athletes in cross country skiing show asthmatic symptoms shows that it is possible to perform in aerobic exercise training even if you have asthma. It is not dangerous to train, not even on a very high level, as long as the asthmatic person is well managed."*

This positive effect of physical activity has been shown also in studies comparing asthmatic patients in GINA step I versus asthmatic patients in GINA step II-III. Both groups had a beneficial effect of physical exercise. Physical activity might of course give rise to bronchoconstriction and coughing among the asthmatic persons, however that is quite easy to manage, and the positive effect outweighs the mentioned negative effects that might occur during exercise, according to associate professor Morten Hostrup.

Data from a systematic meta-analysis that were presented during the symposia (Hansen et al. Eur Respir J 2020; 56: 2000146) including eleven different studies showed that exercise was significantly in favour in relation to asthma control, measured by asthma control questionnaire [ACQ; Total (95% CI) -0.48 (-0.81—0.14)]. A small effect in favour of exercise was also seen for lung function [FEV1, FEV1% and FEV1/FVC; Total (95% CI) -0.36 (-0.72—0.00)], and airway inflammation [FENO and sputum; Total (95% CI) -0.03 (-0.41—0.36].

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Key take aways 1

- Persons with asthma should be physically active.
- Aerobic exercise training improves asthma control and quality of life and may enhance lung function.

There is an increased prevalence of asthma or asthma-related conditions in obese peoples as well as among peoples that are inactive (i.e., “couch potatoes”). Also, for obese asthmatics, physical exercise gives rise to a U-shaped curve when it comes to beneficial effect for asthma or asthma-related conditions. The favourable effects seen in relation to asthmatic peoples in regards to physical exercise are even more pronounced among obese women than obese men. A study presented by the speaker showed that diet restrictions in combination with physical activity had the most favourable effect on obese asthmatic persons.

Key take aways 2

- Inactivity and obesity are associated with a higher prevalence of asthma.
- Physical activity (and diet i.e., to lose weight) improves asthma control.
- However, there is a U-curve; Excessive vigorous training increases the risk of developing asthma and asthma related conditions.

Maria Messerer
Medical Director Nordics

Current evidence of exercise and dietary interventions in asthma

PRESENTED BY MARIUS HENRIKSEN, DENMARK

Wednesday afternoon´s session *"Evidence for physiotherapy"* ended with Prof. Henriksen giving an overview of the relative few randomized controlled trials addressing the effect of exercise and dietary interventions in asthma. A total of ten trials, where six were conducted in adults, were in 2019 reviewed in *Weight Loss of Children and Adults with Obesity and Asthma* by William Okoniewski, Kim D. Lu and Erick Forno published in Ann Am Thorac Soc. Prof. Henriksen highlighted that these trials investigated the role of variable interventions, i.e., counselling, cognitive behaviour therapy, calorie restrictions, exercise, etc. with variable duration, and weight loss obtained (0-15 %). Thereby, it is not possible to conduct meta-analyses and Prof. Henriksen stated clearly that more research is needed. Before turning to his recent work, Prof. Henriksen reminded us that exercise is recognized as treatment for 31 conditions by the Danish health authorities.

Thus, exercise is medicine!

After the statement Prof. Henriksen turned to two recent projects in his group, the EFFORT and the REPLACE projects, looking at the effect of eight weeks high intensity interval training (HIIT) three times weekly on non-obese asthma patients with and without dietary intervention, to investigate whether regular exercise can improve asthma control to an extent where reduction in daily ICS is possible without loss of disease control.

The EFFORT project showed an overall increase in the fitness of the participants in the experimental groups. The group receiving exercise and dietary intervention improved their mean VO_2 max with 5.1 ml/min/kg compared to the control that had no significant improvement compared to baseline. The improvement was mainly driven by the exercise part, consistent with existing literature. Furthermore, all groups had a significant improved asthma control (ACQ-score) compared to baseline when entering the study, and interestingly there was a slight but significant stronger improvement in the exercise + dietary intervention group compared to the control post study.

The REPLACE project included physical inactive (<60 minutes vigorous activity/week) patients with persistent asthma, an ACQ-5 score between 1.0-2.5, and a daily intake of ICS ≥400 µg (Budesonide). Onehundredfifty patients were randomised, with n=102 in the HIIT arm and n=48 in the control arm and followed for 12 months, with ~85% completing the study. An ICS algorithm was applied to determine the stepping up or down in ICS based on ACQ-5 worsening or improvement, respectively. After 12 months the control group had a non-significant reduction of 16 µg ICS compared to baseline and the HIIT group had an additional 314 µg reduction (p=0.0002), corresponding to a 24% reduction in daily intake of ICS. The two groups had comparable FeNO and FEV1 measurements.

The main conclusion drawn from the study is that HIIT in untrained asthma patients give a sustainable and clinically relevant reduction in daily ICS intake without compromising asthma control. Thus, the results are supporting the use of regular high intensity interval training in adults with asthma.

Nicolai Krogh
Medical Science Liaison, Denmark

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Breathlessness in the Nordics

PRESENTED BY MAGNUS EKSTRÖM, SWEDEN

Between 10-20% of the population in Sweden and Norway experience breathlessness during their daily lives, and women are more frequently affected than men. Breathlessness is a feeling and can be described as *"the awareness of problems with breathing"*. The brain predicts what needs to be done, how much muscle work is needed to assure adequate ventilation etc. At the same time, afferent feedback is sent to the brain, and analysed whether these signals match the model of the predicted need. If there is a mismatch, this leads to distress, and the feeling of breathlessness in the person. The presentation shed light on the question whether breathlessness is heritable. Data from the RHINESSA study including 1720 parents and 2476 offspring was analysed. The results showed that 32.7% of parents and 14.7% of offspring reported breathlessness (Ekström et al, Thorax. 2022 Feb;77(2):172-177.) The authors found an independent contribution of factors such as obesity, current smoking, asthma, depression, lower lung function and female sex. There was a higher odds ratio for parents with breathlessness to have offspring who experience breathlessness, too [adjusted OR 1.8 (95% CI 1.1 to 2.9)]. Ekström concludes that despite a need for better read-outs for breathlessness to be included, the ventilatory control system is partly inherited.

Barbara Fuchs
Medical Manager, Nordics

An overview of pulmonary rehabilitation (PR), how it works today, effects of PR interventions, and what we are aiming at in the future

PRESENTED BY MARGARETA EMTNER, SWEDEN

The Wednesday afternoon session *"Evidence for physiotherapy"* started off with Prof. Margareta Emtner from Sweden giving an overview of pulmonary rehabilitation (PR). She presented some of the current evidence of the positive outcomes of PR in COPD, i.e., less dyspnoea, increased quality of life, increased aerobic maximal capacity, increased functional capacity and more muscle strength. In addition, PR after exacerbation leads to less hospitalizations. Hence, it is no longer a question whether PR matters. It does!

However, only 15% of COPD patients get referral to PR. Among the patients that get referral, 8-50% never attends and 20-60% fail to complete. THIS is the problem we are facing today. Prof. Emtner pointed to several factors that contribute to low referral, attendance, and completion of PR:

- few PR programmes exist/few have access to PR programmes
- PR is more complex for the patient than simply taking their medication
- PR requires more from HCPs (potential upskilling is required)
- the setting of PR does not suit the patient (i.e., daily life, economy, etc.)

Prof. Emtner came up with suggestions on how PR should be organized in the future. First, we need more focus on PR as a valuable important treatment. To increase PR referrals, we need to improve the knowledge and skills among HCPs. It is crucial that HCPs know the complexity of living with chronic lung disease, and an interdisciplinary team approach is necessary. Various settings for PR should be offered such as hospital-, community-, home-based and telerehabilitation, or a combination. Further, Prof. Emtner shared her thoughts on what the content of PR should be in the future. PR should include non-pharmacological interventions such as exercise training, education, and behaviour change. It is important to improve self-efficacy, disease-related knowledge, self-management strategies, and decrease social isolation. Moreover, it is important to target extrapulmonary features and more strategies are needed as comorbidities are common.

Finally, PR should be INDIVIDUALIZED!

Ingvild Bjellmo Johnsen
Medical Advisor, Norway

Asthma immunopathology as the determinant of biologic target therapy in severe asthma

PRESENTED BY LENA ULLER, SWEDEN

During the Thursday morning session *"Biologics in asthma"* Prof. Lena Uller from Sweden gave a comprehensive overview of the immunopathology of asthma. Asthma is a heterogenous disease and as an effort to understand the heterogeneity better the concepts asthma phenotypes and asthma endotypes have been introduced. Asthma phenotypes are observable clinical characteristics that result from a combination of hereditary and environmental influences and can be divided into clinical phenotypes and inflammatory phenotypes. Asthma endotypes are based on distinct pathophysiological mechanisms at a cellular and molecular level.

Prof. Uller continued by describing the two best characterized asthma endotypes in more detail; T2-high asthma and T2-low asthma. T2-high asthma is dominated by the classical type 2 cytokines (IL-4, IL-5 and IL-13) and eosinophilic inflammation. T2-low asthma is less understood to date, but involves cytokines like IL-6, IL-8, IL-1β, TNF-α, IFN-γ and IL17A. The latter endotype cluster is typically dominated by neutrophilic inflammation. T2-low asthma may also occur in the absence of both eosinophils and neutrophils. This is often referred to as paucigranulocytic asthma, where mast cells and fibroblasts appear to drive the response. The crucial effector cells of the immunopathological responses in asthma are T helper (Th) cells and the more recently identified innate lymphoid cells (ILCs) class. Where Th2 and ILC2 cells are particularly important in T2-high asthma, Th17 and ILC3 cells seem to be involved in T2-low asthma.

Prof. Uller went on describing the bronchial epithelium as instrumental in asthma. Its position towards the "outer world" makes it our physical and immunological barrier. Here, it plays a central role in initiating innate and adaptive immune responses in the lung (i.e., it is the major cell type being infected with rhinovirus and bacteria). Importantly, it produces a range of mediators, including pro-inflammatory cytokines driving inflammation, anti-viral and anti-microbial substances protecting the body from harm as well as mediators that can induce structural changes leading to airway remodelling.

Respiratory viral infections are a major cause of asthma exacerbations. However, molecular mechanisms are still largely unknown and efficient treatment is lacking. Prof. Uller showed us what is known about the bronchial epithelium in relation to the viral innate immune response. Respiratory viruses, including Rhinovirus, are recognised by pattern recognition receptors (PRRs) on the bronchial epithelium. These PRRs include the endosomal TLR3 and the cytoplasmic receptors RIG-I and MDA5. Upon recognition of virus, the PRRs trigger a signalling cascade in the cells leading to activation

of the transcription factors NF-kB and IRFs which in turn drive the transcription of genes encoding TSLP, IL-33 and IL-25 - and interferons, respectively. Prof. Uller continued her talk focusing on TSLP. She presented research showing that TSLP is overexpressed in response to viral stimulation and evidence for TSLP being expressed on many immune cells and cell types in the airways. She also explained how TSLP plays a key role in driving allergic inflammation (through Th2 cells), in driving eosinophilic inflammation (through ILC2 cells) and proposed how TSLP may play a role in driving neutrophilic inflammation (through Th17 cells). She eventually showed how TSLP can drive structural changes in the airways (through fibroblast proliferation and smooth muscle hypertrophy). Overall, TSLP acts as an epithelial alarmin across the spectrum of inflammation in asthma, which makes it an interesting target for treatment.

Finally, Prof. Uller gave an overview of the immune mechanisms of current asthma biologics, including those targeting IgE, IL-5, IL-4, IL-13 and TSLP.

Ingvild Bjellmo Johnsen
Medical Advisor, Norway

What can pulmonologists learn from palliative care specialists?

PRESENTED BY REETA PIILI, FINLAND

At the Thursday afternoon session *"Palliative care in respiratory diseases"*, Dr. Reeta Piili from Finland shared her thoughts about what pulmonologists can learn from palliative care specialists focusing on five aspects.

First, *symptom management* is essential. We know that respiratory patients have very high symptom burden. It is important to assess symptoms systematically, both physical and psychological symptoms. We should go beyond breathlessness and cough. Fatigue, anxiety, depression, pain, and existential needs are also very important when treating these patients. The different symptoms should be treated both non-pharmacologically and pharmacologically, and it is crucial to document and follow-up on symptoms. Dr. Piili came with a concrete encouragement to apply the Edmonton Symtom Assessment System (ESAS) as a tool to help the overall assessment of patients with respiratory diseases.

Second, *palliative care is a real opportunity*. There is increasing evidence for the positive outcomes of palliative care on symptom burden, quality of life, advance care planning, health-care utilisation, the possibility to die outside hospitals, and on overall patient and caregiver satisfaction.

Third, *decision making* is challenging with respiratory diseases due to the uncertainty concerning prognosis. Often, we do not know if patients will survive exacerbations or if they are going to die from the acute event. Dr. Piili came with examples of decisions that often need to be taken, e.g., invasive vs non-invasive ventilation and when to start advanced care planning. Importantly, research has proved that patients prefer medical professionals to open the dialog about end of life.

Fourth, it is important to pause *and listen to the patient's thoughts and wishes*. What we assume is the need of the patient is often very different from what the patient actually want. Sit down with the patient and his/her closest ones, define the goals of care together and make an appropriate advanced care plan. Importantly, patients are different - the care plan should be individualized.

Fifth, we need to have *courage*. Courage to be able to talk about what really matters in life. Courage to face reality that life comes to an end for each one of us. Courage to talk about death and dying while making our best to enhance quality of life and finally, courage to collaborate.

Ingvild Bjellmo Johnsen
Medical Advisor, Norway

Treatable traits in obstructive lung disease

PRESENTED BY THERESE LAPPERRE , FLORENCE SCHLEICH

I attended the session *"Treatable traits in obstructive lung diseases"* where Therese Lapperre focused on COPD and Florence Schleich focused on asthma.

Both diseases are complex, heterogenous and characterized by several different factors. Traditionally, clinical guidelines have advocated a stepwise approach to pharmacotherapy of asthma and COPD but there is a need for a more patient-centric, personalized, and precise management approach. The treatable traits strategy has been proposed as a further step towards precision medicine in the management of chronic airway disease, both in stable phase and acute exacerbations.

A treatable trait can be defined as a therapeutic target identified by phenotypes or endotypes through a validated biomarker and it should fulfil three characteristics:

- be clinically relevant and associated with specific disease outcomes (symptoms, health status, risk of future events),
- be easily identifiable and measurable (typically would be a biomarker), and
- be treatable (should be effectively treated and this effect should ideally be measured in RCT).

The treatable traits can be divided into three main groups: pulmonary, extrapulmonary and behavioral/lifestyle.

In **Therese Lapperre´s** presentation, she focused on different types of treatable traits targeting different COPD phenotypes and endotypes identified by biomarkers. As an example, she referred to Barnes et al. (Allergy 2019 Jul;74(7):1249-1256.) focusing on inflammatory endotypes in COPD, where the problem with treating the underlying inflammation is brought up. Most patients have increased levels of neutrophils in sputum or increased levels of eosinophiles in sputum and blood. The neutrophilic inflammation has shown to be unresponsive to corticosteroids even in high doses. The lack of responsiveness to ICS is reflected by mortality and progression of COPD. On the other hand, increased blood eosinophils (>300/µL or >4%) and sputum eosinophils are associated with more frequent exacerbations and predict a good response to corticosteroids in reducing and treating acute exacerbations. Therese also referred to the IMPACT-study demonstrating that assessment of blood eosinophil count and smoking status had the potential to optimize ICS (as part in dual and triple therapy) use in clinical practice in patients with COPD and a history of exacerbations (Pascoe et al., Lancet Respir Med. 2019 Sep;7(9):745-756). Furthermore, in the ETHOS-trial the incidence of death was also analyzed according to blood eosinophil count where a tendency of a beneficial effect of Budesonide/Glycopyrrolate/Formoterol versus glycopyrrolate/formoterol fumarate in reducing mortality generally increased with eosinophil count (Martinez et al., Am J Respir Crit Care Med. 2020 Mar 1;203(5):553-564).

Other examples of biomarkers that can be used as treatable traits are biomarkers for bacteria-, virus, or eosinophil-associated exacerbations of COPD. Bafadhel et al., (Am J Respir Crit Care Med 2011, Sep 15;184(6):662-71) showed that these biomarkers can be used to identify specific clinical phenotypes during exacerbations of COPD.

As extra pulmonary traits, the impact of comorbidities of COPD was mentioned, as these comorbidities contribute to morbidity and mortality of the patients and impact the health care system. It is therefore of importance to identify comorbidities. These patients need an individual and tailored treatment and care (Vanfleteren et al., Eur Respir J. 2017 Feb 8;49(2):1601696), which is mentioned in the NICE guidelines.

Examples of behavioral and lifestyle treatable traits are social behaviors (e.g. social support and network), smoking and other environmental exposures and inhalations technique. For example, smokers and ex-smokers are less responsive to ICS and roflumilast (Singh D, et al. Am J Respir Crit Care Med. 2020). Furthermore, regarding inhalation technique, the use of one inhalation device is preferable over several since it resulted in more patients gaining health status improvement and greater lung function improvement (Halpin et al., ERJ Open Res. 2021 Jun 7;7(2):00950-2020).

To maximize treatment for COPD patients, McDonald et al. (Thorax. 2013 Jul;68(7):691-4), have suggested a multidimensional assessment and tailored interventions for COPD.

In the next part of the session **Florence Schleich** presented treatable traits in asthma, where several of the biomarkers mentioned for COPD also are relevant for asthma. She began by presenting a study published in 2008 by Haldar et al., (Am J Respir Crit Care Med. 2008 Aug 1;178(3):218-224.) where a cluster analysis was performed to classify patients with asthma into phenotypic groups mainly based on symptoms and eosinophilic inflammation that exhibit differences in clinical response to treatment with corticosteroids. The study supported a role for the use of multivariate techniques in the classification of asthma populations leading to optimal treatment.

Furthermore, she focused on the level of eosinophiles in relation to e.g. risk of exacerbations, asthma control, polyps and decline in lung function. For example, by analyzing the sputum of general population of asthma (Schleich et al., BMC Pulm Med. 2013 Feb 26;13:11) and sputum of persons with severe asthma (Schleich et al., Respir Med 2014 Dec;108(12):1723-32), different patterns of inflammatory phenotypes were noticed. In both populations the eosinophilic and paucigranulocytic phenotype are the most frequent, although the level of eosinophilia was higher in the general asthma group. In the severe asthma group the majority displayed indices of persistent airflow limitation despite high-dose corticosteroids. Treatment with ICS normalized the eosinophilic inflammation and resulted in better asthma control, reduced risk of exacerbations and reduced hospitalizations (Green et al., Lancet. 2002 Nov 30;360(9347):1715-21).

Furthermore, exhaled nitric oxide to predict risk of asthma attacks was given as example of a treatable trait, as well as airflow limitation and airway infections. Airflow limitation can be caused by mucus plugs and can easily be measured with a PEF-meter and CT scan, and be treated with LAMA and LABA (Dunican et al., J Clin Invest. 2018 Mar 1;128(3):997-1009). The most important extrapulmonary treatable traits are smoking, obesity, obstructive sleep apnea, gastroesophageal reflux and anxiety and depression. Some of these extrapulmonary treatable traits are easy to treat e.g. obesity by changed diet and gastroesophageal reflux with PPIs, but pollution or bad working environment could be more difficult to target.

To sum up this session, COPD and asthma are heterogenous and complex diseases. The treatable traits strategy is a step towards a more personalized and individualized precision medicine to optimize the treatment in patients with chronic airway diseases. Treatable traits should be clinically relevant, identifiable, measurable and treatable and include pulmonary, extrapulmonary and behavioral treatable traits.

Jenny Johansson
Medical Advisor, Sweden

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Respiratory disease and reproduction

CHAIRED BY CHARLOTTE ULRIK, FRANCISCO GOMEZ REAL

During the Friday morning session chaired by Charlotte Ulrik and Francisco Gomez Real, the participating authors discussed various aspects of reproduction in the context of lung diseases. To name a few, Paula Kauppi, Finland, described different cytokine networks and their role during pregnancy. Type 1 cytokines play a role in implantation and the initiation of labour, Type 2 cytokines are involved in placental development and tissue integrity, and Type 3 cytokines in the maintenance

of pregnancy. Asthma in adults is more common in women, and approximately 10% of pregnant mothers have asthma. But are atopic persons perfect mothers? In her presentation, Paula Kauppi presented data showing an association of maternal asthma with eg. preterm birth and low birth weight. Asthma medication reduced the risk of preterm birth. Later during the session, Anne Vejen Hansen, Denmark, presented data on the association of asthma and infertility. Both asthma and infertility are among the most common disorders in young adults. Women with asthma have a longer time to pregnancy when treated for infertility than women without asthma (mean time to pregnancy 55 months versus 34 months). Moreover, women with asthma are more likely to require fertility treatment than women without asthma (odds ratio 2.12), however the association of the need for fertility treatment with asthma treatment was low for ICS+LABA (Crowe et al., Clinical Epidemiology 2020 ,12:579-587). Casper Tidemandsen, Denmark, presented analyses on asthma and the risk for recurrent pregnancy loss. He presented data emphasising the importance of well controlled asthma even during pregnancy, as the use of ICS was not related to the risk of recurrent pregnancy losses, while the frequent use of SABA increased the odds ratio for pregnancy losses in asthmatics. During the presentation by Erik SH Hansen, Denmark, asthma was discussed in the context of hormone replacement therapy. The observation of a late onset asthma phenotype in females let to the hypothesis that it is related to menopause and a decline in oestrogen levels. If that was the case, women on hormone replacement therapy should have a lower incidence of asthma, the author speculated. However, the data showed that the opposite was the case: the incidence of asthma was significant higher in women receiving hormone replacement therapy. Half of these new cases of asthma occurred during the first years of hormone replacement therapy. Women who had a diagnosis of asthma before hormone replacement therapy was initiated however experienced no differences in the dose of ICS prescribed to control their disease compared to women not receiving hormone replacement therapy.

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